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ORIGINAL REPORT

Bendamustine in Combination With Gemcitabine and Vinorelbine Is an Effective Regimen As Induction Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma: Final Results of a Multicenter Phase II Study

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ABSTRACT

Purpose
This multicenter, open-label, phase II study evaluated the combination of bendamustine, gemcitabine, and vinorelbine (BeGEV) as induction therapy before autologous stem-cell transplantation (ASCT) in patients with relapsed or refractory Hodgkin lymphoma (HL).

Patients and Methods
Patients with HL who were refractory to or had relapsed after one previous chemotherapy line were eligible. The primary end point was complete response (CR) rate after four cycles of therapy. Secondary end points were: overall response rate, stem-cell mobilization activity, and toxicity. Progression-free and overall survival were also evaluated.

Results
In total, 59 patients were enrolled. After four cycles of therapy, 43 patients (73%) achieved CR, and six (10%) achieved partial response, for an overall response rate of 83%. The most common grade 3 to 4 nonhematologic toxicities included febrile neutropenia (n = 7) and infection (n = 4). Regarding hematologic toxicities, grade 3 to 4 thrombocytopenia and neutropenia were each experienced by eight patients (13.5%). CD34+ cells were successfully harvested in 55 of 57 evaluable patients, and 43 of 49 responding patients underwent ASCT. With a median follow-up of 29 months, the 2-year progression-free and overall survival rates for the total population were 62.2% and 77.6%, respectively. The same figures for patients undergoing autograft were 80.8% and 89.3%, respectively.

Conclusion
This phase II study demonstrates that BeGEV is an effective salvage regimen able to induce CR in a high proportion of patients with relapsed or refractory HL before ASCT. These data provide a strong rationale for further development of the BeGEV regimen.

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INTRODUCTION

First-line chemoradiotherapy yields cure rates approaching 80% in patients with advanced-stage Hodgkin lymphoma (HL).[1,2] Patients who are refractory to or relapse after initial therapy usually have a worse prognosis, and second-line salvage treatment programs are required as early as possible to reduce the risk of treatment failure, avoid unnecessary toxicity, and prolong survival.[3] Two randomized, phase III studies conducted more than 10 years ago showed an improved failure-free survival rate with high-dose chemotherapy and autologous stem-cell transplantation (ASCT) compared with conventional-dose chemotherapy.[4,5] However, the efficacy of this approach has been challenged by a recent meta-analysis.[3] Therefore, further investigation of the optimal therapeutic strategy in patients with relapsed or refractory HL seems warranted.[6,7]

Achieving complete response (CR) after induction chemotherapy administered before ASCT represents the strongest prognostic factor in

patients receiving second-line salvage chemotherapy.[8] Thus, increasing the rate of CR achieved with induction chemotherapy represents a primary goal in patients with refractory or relapsed HL.

Our group developed the IGEV regimen, consisting of ifosfamide, gemcitabine, and vinorelbine, as pretransplantation salvage chemotherapy.[8] In a study of 91 patients, the overall response rate (ORR) was 81%, with a 54% CR rate and no toxicity concerns.[8] Furthermore, the IGEV regimen demonstrated excellent mobilizing potential of peripheral-blood stem cells.[9]

Bendamustine hydrochloride comprises a 2-chloroethylamine alkylating group and a benzimidazole ring similar to cladribine. Despite its structural similarities to both alkylating agents and purine analogs, the exact mechanism of action of bendamustine is unknown.[10] Retrospective and prospective studies have shown promising activity of bendamustine monotherapy in the treatment of patients with multirelapsed HL who were ineligible ASCT or for whom ASCT had failed, with a remarkable incidence of CR (range, 25% to 35%).[11-15] The use of bendamustine in combination regimens as second-line salvage chemotherapy in patients with relapsed or refractory HL has been proposed to increase the CR rate.[11] Therefore, in this multicenter phase II study, we replaced ifosfamide in the IGEV regimen with bendamustine to evaluate this combination (BeGEV) as induction therapy before ASCT in patients with relapsed or refractory HL.

PATIENTS AND METHODS

Patient Eligibility

Consecutive patients with HL age 18 years or older who were refractory to or had relapsed after receiving one previous chemotherapy line were eligible. Refractory disease was defined as disease progression during or within 3 months of doxorubicin-based chemotherapy, and relapsed disease was defined as reappearance of disease after CR lasting 3 months or longer.[16] Other inclusion criteria were as follows: Eastern Cooperative Oncology Group performance status $\alpha\tau 2$ or lower, at least one site of measurable nodal disease at baseline of 1.5 cm or larger, absolute neutrophil count of 1.5×10^9/L or greater, platelet count of 75×10^9/L or greater, and negative pregnancy test and agreement on using a method of contraception for women. Patients were excluded if they had received radiation therapy 3 weeks or less before study entry, had evidence of other malignancies or history of malignancy within the 3 years before study entry, had abnormal biochemical tests (creatinine $\geq 1.5 \times$ ULN, bilirubin $\geq 1.5 \times$ ULN, or AST/ALT $\geq 2.5 \times$ ULN or $\geq 5.0 \times$ ULN if transaminase elevation was due to disease involvement), or had ongoing HIV, hepatitis B virus, or hepatitis C virus infection.

Setting and Study Design

This was a prospective, open-label, multicenter phase II study. Ten centers from the Fondazione Italiana Linfomi (Italian Lymphoma Foundation), located all over the Italian territory, participated in this study, which started in September 2011 and ended in March 2014. The study was conducted in accordance with the Helsinki Declaration; the ethical committees of the participating centers approved the study protocol. All patients signed an informed consent before inclusion.

Study Treatment

The BeGEV regimen consisted of gemcitabine 800 mg/m^2 on days 1 and 4, vinorelbine 20 mg/m^2 on day 1, and bendamustine 90 mg/m^2 on days 2 and 3. Prednisolone 100 mg per day was administered on days 1 to 4. Patients received four cycles of the BeGEV regimen administered every 21 days. Growth factor support with granulocyte colony-stimulating factor (G-CSF) was administered at each cycle. Patients received *Pneumocystis* pneumonia prophylaxis and antiemetics in accordance with institutional guidelines. Treatment was interrupted in case of disease progression, unacceptable toxicity, or withdrawal of consent. Patients who achieved CR or partial response (PR) after completion of the planned four cycles received myeloablative therapy with BEAM (carmustine, etoposide, cytarabine, and melphalan; n = 20) or FEAM (fotemustine, etoposide, cytarabine, and melphalan; n = 23) followed by reinfusion of mobilized CD34+ circulating stem cells. BEAM consisted of carmustine 300 mg/m^2 on day −6, etoposide 200 mg/m^2 on days −5 to −2, cytarabine 400 mg/m^2 intravenously (IV) on days −5 to −2, and melphalan 140 mg/m^2 IV on day −1. FEAM consisted of fotemustine 150 mg/m^2 IV on days −7 and −6, etoposide 200 mg/m^2 on days −5 to −2, cytarabine 400 mg/m^2 IV on days −5 to −2, and melphalan 140 mg/m^2 IV, on day −1. Both myeloablative regimens were followed by the reinfusion of at least 2×10^6 per kilogram of body weight of CD34+ cells on day 0 and G-CSF 5 μg/kg subcutaneously per day from day +5 until achievement of WBC of 3,000/μL or greater for 3 days. Patients with residual lymphoma (> 1.5 cm on computed tomography [CT] scan) at 100 days after ASCT received 30-Gy involved-field radiotherapy.

Response Criteria

Responses were assessed according to the International Working Group response criteria.[17] CT and [^{18}F]fluorodeoxyglucose–positron emission tomography scans were performed before and after the fourth BeGEV cycle. According to the 2007 criteria of Cheson et al,[17] a metabolic response was scored as CR when positron emission tomography scan results were negative on the basis of visual analysis, independent from the presence of residual masses on CT scan.

CD34+ Cell Mobilization and Collection

To elicit CD34+ cell mobilization, G-CSF (10 μg/kg body weight) was administered once per day beginning on day 7 and continued until completion of the target cell harvesting (3×10^6 CD34+ cells/kg). Collection of CD34+ cells was usually performed after the first or second cycle, when circulating CD34+ cells were 10/μL or greater using a COBE Spectra separator (COBE, Lakewood, CO).

Data Analysis

The primary end point was CR proportion after four cycles of therapy. Secondary end points were: ORR (ie, CR plus PR), stem-cell mobilization activity, and toxicity (graded according to Common Terminology Criteria for Adverse Events [version 4.0]). Progression-free (PFS; calculated from first BeGEV administration to disease progression, relapse, or death, whichever occurred first, or until last disease assessment for patient alive and without progressive disease) and overall survival (OS; calculated from first BeGEV administration to death or last contact) were also evaluated. The sample size was estimated using a Fleming's single-stage phase II design. A CR proportion of 50% or lower was considered to be clinically unworthy, whereas a proportion of 65% or higher would be assumed to be of potential interest. The drug would be recommended for further study, with a 10% rejection error (one sided) and a power of 85%, if 35 or more of the 59 total patients were to achieve CR. Data were analyzed by descriptive statistics. Differences between groups were estimated with the χ^2 or Fisher's exact test as appropriate. Kaplan-Meier survival curves were estimated, and the log-rank test was used to assess survival differences. The univariable Cox proportional hazards regression model was used to calculate hazard ratios (HRs) with 95% CIs. Statistical significance was set at P less than .05 (two sided) for all secondary evaluations. Statistical analysis was performed using STATA software (version 13; STATA, College Station, TX).

RESULTS

Patient Characteristics

Between September 2011 and March 2014, 59 patients were enrolled (Table 1; Fig 1). The median age was 33 years (range, 18 to 68 years), and 31 patients (53%) were men. Fifty-six patients (95%) had received ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as first-line therapy, and three (5%) had received BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone). Overall, 27 patients (46%) were refractory to and 32 (54%) had experienced relapse after first-line treatment (22 within and 10 after 12 months). Of the 59 patients, one was not evaluable for response. This patient discontinued the study after two cycles of BeGEV because of psychiatric and behavioral problems while he was in clinical response; he was subsequently monitored and died as a result of disease progression.

Treatment Response and ASCT

By intention to treat, after four cycles of therapy, 43 patients (73%) achieved CR, and six (10%) achieved PR, for an ORR of 83% (49 of 59; Fig 1). One patient (2%) had stable disease, eight patients (14%) experienced disease progression, and one patient (2%) was not evaluable for response (Table 2). In univariable analysis, the only factor associated with a different probability of achieving CR was disease status at study entry, with CR being achieved by 84% of patients with relapsed disease and 59% of those with refractory disease ($P = .031$; Table 2). Of the 49 responding patients, 43 (73% by intention to treat) proceeded to ASCT (38 of 43 achieving CR and five of six achieving PR); the remaining six patients did not proceed to ASCT because of mobilization failure (n = 2), physician decision (n = 2), early relapse (n = 1), and patient refusal (n = 1).

Table 1. Patient Demographic and Clinical Characteristics (N = 59)

Characteristic	No.	%
Age, years		
Median	33	
Range	18-68	
Sex		
Male	31	53
Female	28	48
Response to primary therapy		
Relapsed disease	32	54
CR < 1 year	22	37
CR ≥ 1 year	10	17
Primary refractory	27	46
Extranodal sites of disease		
Yes	24	41
No	35	59
Prior radiotherapy		
Yes	9	15
No	50	85
Prior chemotherapy		
ABVD	56	95
BEACOPP	3	5

NOTE. Sums of percentages may not be equal to 100% as a result of rounding.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; CR, complete response.

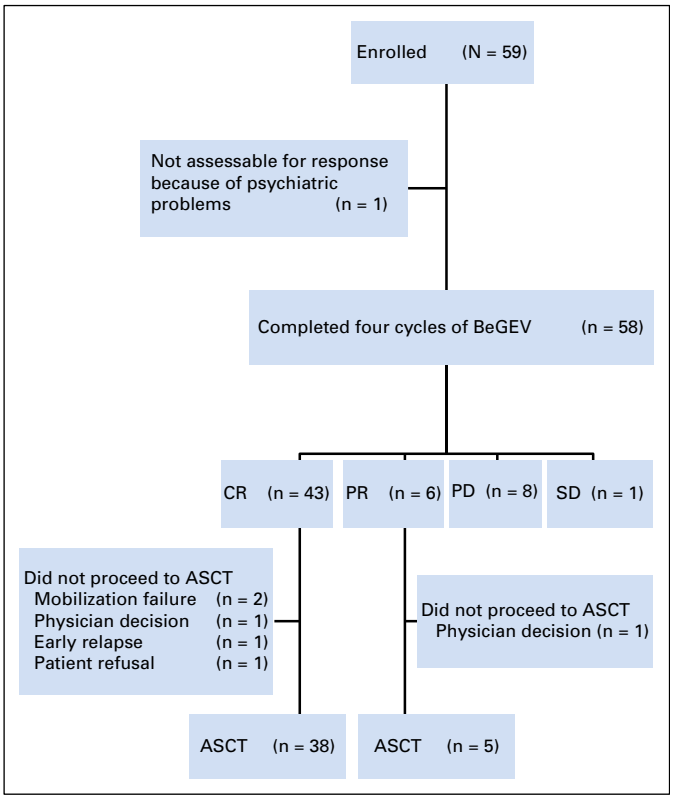

Fig 1. Diagram showing the flow of participants. ASCT, autologous stem-cell transplantation; BeGEV, bendamustine, gemcitabine, and vinorelbine; CR, complete remission; PD, progressive disease; PR, partial remission; SD; stable disease.

Survival Analysis

PFS and OS Kaplan-Meier curves for all patients are shown in Figs 2A and 2B. With a median follow-up of 29.1 months (range, 3.4 to 49.1 months), the 2-year PFS and OS rates were 62.2% and 77.6%, respectively. No differences were observed when main prognostic factors were analyzed. In particular, response to first-line chemotherapy did not significantly influence prognosis, with a 2-year PFS of 62.5% veresus 62.3% ($P = .769$) and 2-year OS of 79.7% versus 75.9% ($P = .645$) for patients with relapsed and refractory disease, respectively (Figs 2C and 2D). The 2-year PFS and OS rates for patients receiving an autograft during CR or PR were 80.8% and 89.3%, respectively (Figs 2E and 2F).

CD34+ Cell Mobilization and Harvesting

Fifty-seven of 59 patients were evaluable for CD34+ cell mobilization. Two patients were excluded: one because of medical decision and one for stem-cell collection before study inclusion. After BeGEV, the median peak value of CD34+ cells (89 cells/μL; range, 1 to 763 cells/μL) was recorded on day 12. Mobilization failure was detected in two (3.5%) of 57 patients; CD34+ cells were successfully harvested in 55 (96.5%) of 57 evaluable patients. Forty-two patients (76%) required one leukapheresis to harvest the planned target CD34+ cell yield (3×10^6 CD34+ cells/kg body

Table 2. Clinical Responses to BeGEV Regimen According to ITT and Disease Status at Entry

Parameter	No. of Patients	CR		PR		SD		PD		NE	
		No.	%	No.	%	No.	%	No.	%	No.	%
Response by ITT	59	43	73	6	10	1	2	8	14	1	2
Disease status at study entry											
Relapsed	32	27	84*	3	9	1	3	0	0	1	3
Refractory	27	16	59*	3	11	0	0	8	30	0	0

NOTE. One patient discontinued the study after two cycles of BeGEV because of psychiatric and behavioral problems while he was clinically responding. Two patients were evaluated after the third cycle (but not the fourth), but they continued the study according to protocol. Sums of percentages may not be equal to 100% as a result of rounding.

Abbreviations: BeGEV, bendamustine, gemcitabine, and vinorelbine; CR, complete response; ITT, intention to treat; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

*P = .031 (CR *v* other).

weight), whereas 13 patients (24%) required two leukaphereses. The median total yield of CD34+ cells per kilogram of body weight was 8.8×10^6 CD34+ cells (range, 3 to 56×10^6 cells). After ASCT, engraftment of neutrophils and platelets was recorded on median day 11 (range, day 9 to 21) and median day 12 (range, day 9 to 26), respectively.

Toxicity

Adverse events are listed in Table 3. The most common nonhematologic toxicities included grade 1 to 2 nausea, infection, and febrile neutropenia as well as grade 3 to 4 febrile neutropenia (n = 7) and infection (n = 4). Among hematologic toxicities, grade 3 to 4 thrombocytopenia and neutropenia were each experienced by eight patients. Of 223 evaluated cycles, 69 cycles (31%) were delayed because of hematologic toxicity (n = 4), nonhematologic toxicity (n = 5), infection (n = 6), patient-related logistic reasons (n = 49), and other reasons (n = 5). Dose reductions were recorded in 19 cycles (9%) because of poor performance status (n = 1), neutropenia (n = 1), vertigo (n = 1), body weight changes (n = 12), and unknown reasons (n = 4). RBC transfusions were required by 14% (n = 8) and platelet transfusions by 5% of patients (n = 3), respectively. Overall, the median dose-intensity per cycle was more than 98%.

DISCUSSION

This is the first phase II trial to our knowledge reporting efficacy and toxicity data of a novel bendamustine-containing regimen, namely the BeGEV regimen, administered in an outpatient setting to ASCT-eligible patients with HL who were refractory to or experienced relapse after first-line chemotherapy. Notwithstanding the poor prognostic features of study patients, including primary chemotherapy refractoriness (47%), CR duration of less than 1 year (37%), and extranodal disease (41%), the analysis of clinical response clearly shows the remarkable efficacy of this bendamustine-containing regimen as well as its favorable toxicity profile. Notably, the BeGEV regimen induced a 73% CR proportion, which was far higher than the threshold applied to define clinical interest (65%). This CR rate is substantially higher than that reported for the IGEV regimen (73% *v* 54%)[8] and has never to our knowledge been observed using a variety of second-line salvage regimens (eg, ICE [ifosphamide, carboplatin, and etoposide],[18] DHAP [dexamethasone, cisplatin, and cytarabine],[19] or GDP [gemcitabine, dexamethasone, and cisplatin][20]) before ASCT. Additionally, 88% of the patients who responded to the BeGEV regimen were able to proceed to ASCT, showing 2-year PFS and OS rates of 81% and 89%, respectively.

Despite the sample size of our study, which did not allow performance of a multivariable analysis, it seems that completion of the salvage program (BeGEV plus ASCT) overcame the negative prognostic impact of disease status before BeGEV, as shown by lack of significant differences in terms of 2-year PFS and OS in patients with relapsed or refractory disease. However, future studies with larger series will be required to address this issue definitively.

The BeGEV regimen had excellent stem-cell mobilization activity, with only two mobilization failures detected in more than 57 mobilized patients. All patients experienced full hematopoietic engraftment, strongly supporting that BeGEV-mobilized CD34+ cells are fully functional. Thus, these results not only clearly demonstrate that the BeGEV regimen has potent stem-cell mobilizing activity, but also demonstrate that bendamustine does not have any detrimental effect on stem-cell mobilization or stem-cell engraftment.

BeGEV showed a favorable toxicity profile, characterized by limited occurrence of grade 3 to 4 nonhematologic and hematologic toxicities, similar to that observed with the IGEV regimen, without hemorrhagic cystitis. Even more interestingly, BeGEV was administered as an outpatient regimen, further supporting an advantage over other regimens, including IGEV,[8] DHAP,[19] and ICE[18] regimens, which require hydration and hospitalization.

Recently, a variety of novel agents have become available for transplantation-eligible patients with HL as well as patients with relapsed or refractory HL,[21] thus raising the question of whether to incorporate novel agents into conventional chemotherapy regimens or compare these two treatment modalities to optimize treatment strategies for relapsed and refractory HL. Unprecedented efficacy data have been reported for novel agents such as brentuximab vedotin,[22-26] nivolumab,[27-29] and pembrolizumab,[30,31] which target tumor or microenvironmental cells through distinct mechanisms of action. Novel agents have mainly been explored in the setting of ASCT failure, and their use has resulted in CR rates that are far below those observed with the BeGEV regimen in the pretransplantation setting; in contrast, limited data are available on the use of new agents in the pretransplantation

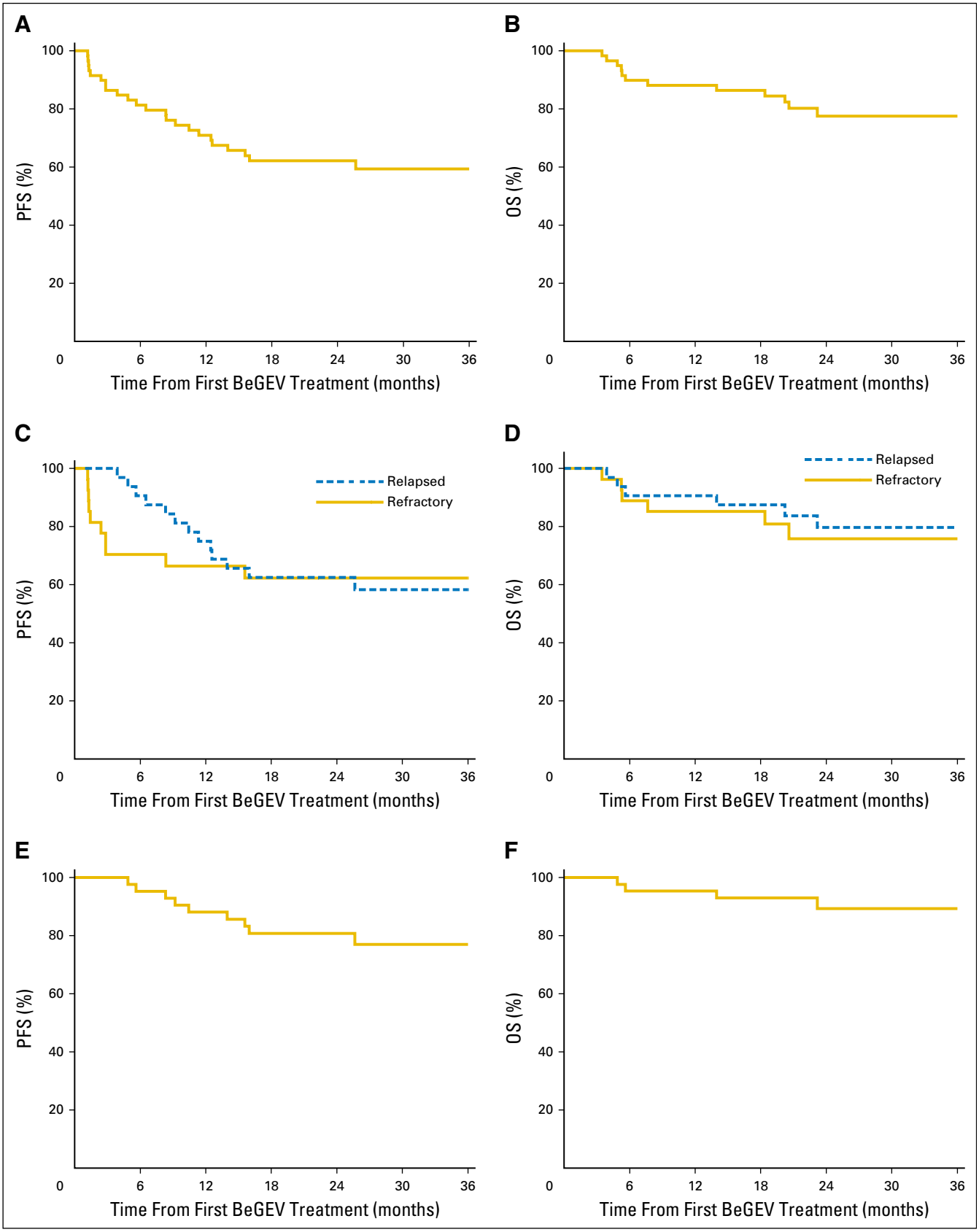

Fig 2. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS) of the overall population, (C) PFS and (D) OS of patients with relapsed or refractory disease before BeGEV (bendamustine, gemcitabine, and vinorelbine), and (E) PFS and (F) OS of patients who achieved complete or partial response and underwent autologous stem-cell transplantation.

Table 3. Adverse Events

Toxicity	No. of Patients (%)	
	Grade 1 and 2	Grade 3 and 4
Anemia	3 (5)	2 (3)
Neutropenia	1 (2)	8 (14)
Thrombocytopenia	0 (0)	8 (14)
Febrile neutropenia	5 (8)	7 (12)
Infection	9 (15)	4 (7)
Nausea	10 (17)	4 (7)
Fatigue	5 (8)	0 (0)
Skin rash	6 (10)	0 (0)
AST/ALT increase	7 (12)	2 (3)

setting.[32-34] Nonetheless, such cross-trial comparisons do not permit firm conclusions to be made regarding the relative efficacy of brentuximab vedotin or nivolumab as compared with the BeGEV regimen.

In conclusion, the results of this multicenter phase II study demonstrate that BeGEV is an effective salvage regimen able to induce CR in a high proportion of patients with relapsed or refractory HL before ASCT. These findings provide a strong rationale for further development of the BeGEV regimen. Because the number of novel agents that may be added in the pretransplantation therapy setting is growing, direct comparisons of combinations incorporating novel agents with BeGEV and other regimens will be necessary to identify the best salvage strategy for relapsed and refractory HL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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